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☐ 1: J Biol Chem. 1993 Apr 25;268(12):8529-35.

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Identification of potential active-site residues in the human poly(ADP-ribose) polymerase.

Simonin F, Poch O, Delarue M, de Murcia G.

Unité propre de recherche de Cancérogénèse et de Mutagenèse Moléculaire et Structurale, Centre National de la Recherche Scientifique, Strasbourg, France.

The carboxyl-terminal catalytic domain of the human poly(ADP-ribose) polymerase (PARP) exhibits sequence homology with the NAD(P)(+)-dependent leucine and glutamate dehydrogenases. To clarify the role played by some conserved residues between PARP and NAD(P)(+)-dependent dehydrogenases, point mutations were introduced into the whole enzyme context. Non-conservative mutations of Lys-893 (K893I) and Asp-993 (D993A) completely inactivate human PARP, whereas conservative and nonconservative mutations of Asp-914 (D914E and D914A, respectively) and Lys-953 (K953R and K953I, respectively) partially alter PARP activity. The consequences of conservative substitution of Lys-893 and Asp-993 on the kinetic properties of human poly(ADP-ribose) polymerase enzyme and the polymer it synthesizes suggest that these 2 amino acids are directly involved in the covalent attachment of the first ADP-ribosyl residue from NAD⁺ onto the acceptor amino acid. In addition, the recent resolution of the three-dimensional structure of the NAD(+)-linked glutamate dehydrogenase from *Clostridium symbiosum* (Baker, P.J., Britton, K.L., Engel, P.C., Farrants, G.W., Lilley, K.S., Rice, D.W., and Stillman, T.J. (1992) *Proteins* 13, 75-86) strongly supports our alignment with leucine and glutamate dehydrogenases and provides an interesting structural framework for the analysis of our results of site-directed mutagenesis.

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